LA GRAVIDANZA DOP
OVODONAZIONE: STIM
RISCHIO OSTETRICO E PERINATALE

Comacchio 18 ottobre 2019

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Ferrara

DOTT.SSA CLAUDIA GUARALDI
U.O. OSTETRICIA E GINECOLOGIA
CENTO (FE)

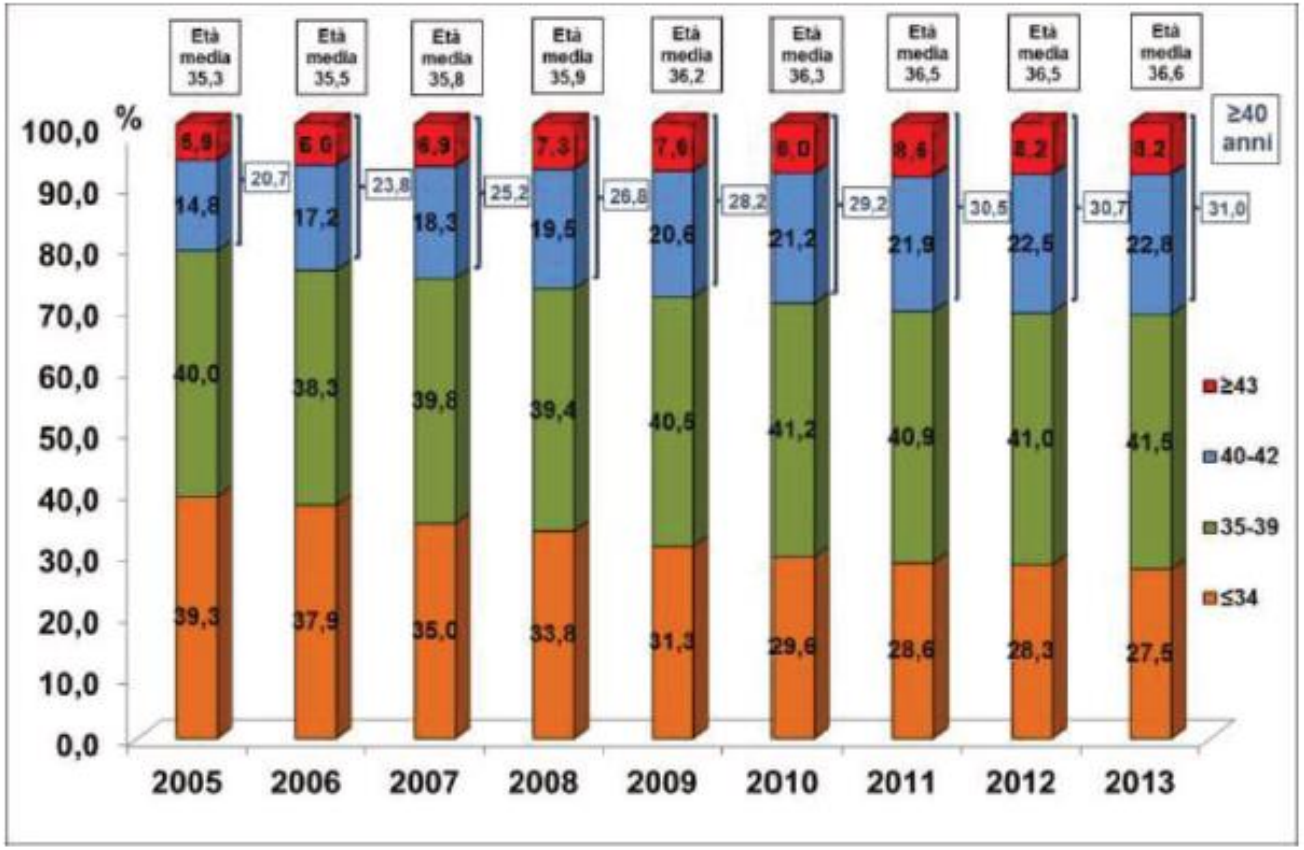
Convegno Nazionale
Fertilità di Coppia:
"Ri"Parliamone

Comacchio (FE)
18 ottobre 2019
Palazzo Bellini

OVODONAZIONE

- Procedura di PMA in cui per ottenere l'embrione si utilizza un ovocita proveniente da donatrice
- La prima procedura di PMA portata a termine con successo è stata effettuata nel 1984
- Ad oggi l'ovodonazione viene utilizzata non solo in caso di premature ovarian failure, ma anche in caso di diminuita riserva ovarica, fallimento di tecniche di PMA etc
- Dal 1984 ad oggi centinaia di gravidanza ottenute con ovodonazione sono state portate a termine, in Europa oltre 39000 di cui la metà in Spagna, ma cominciano ad apparire alcune complicanze ostetriche e perinatali che sembrano correlate proprio all'utilizzo di ovociti donati

Progressivo aumento dell'età media delle pazienti che accedono alla PMA



Dati Ministero della Salute

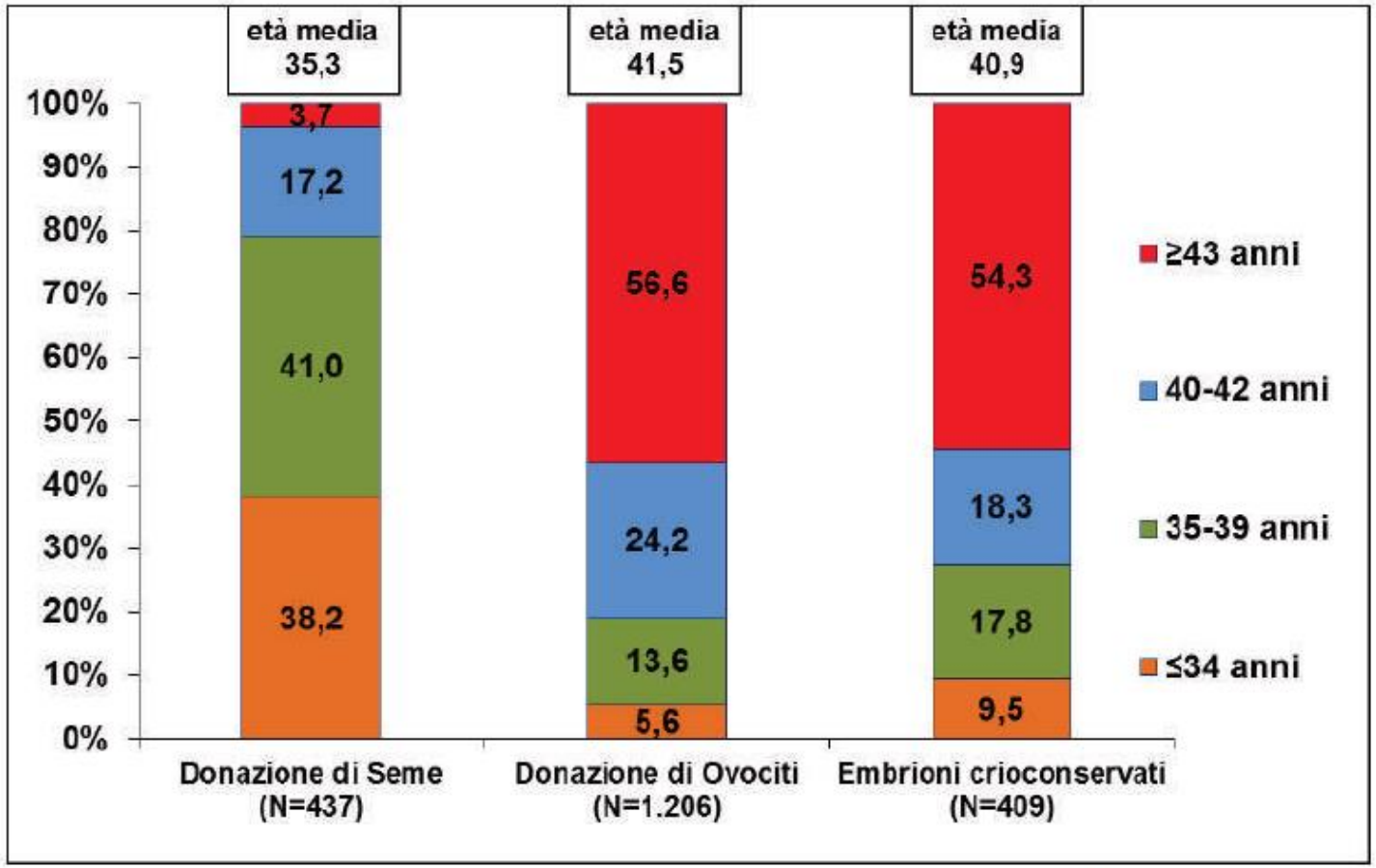
… e l'ovodonazione è vero ha reso possibile ottenere una gravidanza in età peri ed a volte postmenopausali

L'ovodonazione è stata legalizzata in Italia con la Sentenza della Corte Costituzionale del 2014

Superamento del limite biologico della menopausa

La gravidanza è teoricamente possibile a qualunque età

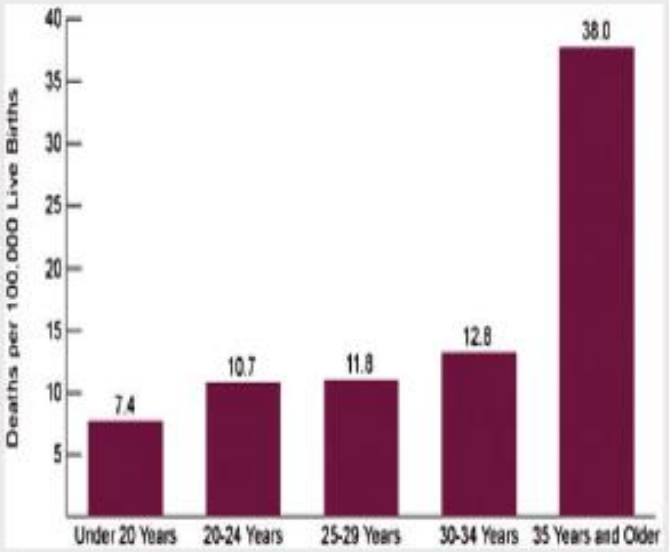
ETÀ MEDIA DELLE PAZIENTI CHE EFFETTUANO OVODONAZIONE



Relazione Ministeriale 2017

ETÀ RIPRODUTTIVA E RISCHIO OSTETRICO

Le donne in età riproduttiva avanzata soffrono comunemente di molte più patologie, a rischio di peggioramento durante la gravidanza, rispetto alle donne giovani



Maternal mortality rates by age in the United States as reported to the CDC and Prevention 2005. Source: US Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child health Bureau. Women's Health USA 2008.

Sauer. Reproduction at advanced maternal age. Fertil Steril 2015

Mortalità materna in relazione all'età

Medical and obstetric events present at the time of delivery among women aged 35–44 y (n = 1,836,403) and aged ≥45 y (n = 23,807) compared with women aged <35 y (n = 10,768,536), Nationwide Inpatient Sample, years 2008–2010.

Condition/event	Age 35–44 y	Age ≥45 y
Medical condition		
Maternal death	2.07 (1.78–2.40)	9.90 (5.60–15.98)
Transfusion	1.21 (1.20–1.23)	2.46 (2.27–2.68)
Myocardial infarction	4.05 (3.29–4.98)	21.38 (11.46–39.88)
Cardiac arrest	2.07 (1.80–2.42)	10.84 (6.48–18.14)
Pulmonary embolism	1.83 (1.69–1.98)	5.01 (3.47–7.23)
Deep vein thrombosis	2.02 (1.91–2.14)	4.38 (3.26–5.89)
Acute renal failure	1.86 (1.76–1.97)	6.38 (5.06–8.04)
Obstetric event		
Cesarean delivery	1.62 (1.61–1.62)	2.51 (2.44–2.57)
Gestational diabetes	2.42 (2.41–2.44)	3.5 (3.37–3.62)
Gestational hypertension	1.11 (1.10–1.12)	2.17 (2.09–2.25)
Preterm labor	1.16 (1.15–1.17)	1.91 (1.84–1.98)
Fetal growth restriction	0.92 (0.91–0.93)	1.53 (1.42–1.64)
Fetal demise	1.30 (1.27–1.33)	2.53 (2.22–2.89)
Premature rupture of membranes	1.10 (1.09–1.11)	1.38 (1.30–1.46)

Note: Values are odds ratio (95% confidence interval). Modified from reference (12). All *P* values < .001 compared with women aged <35 y.

Sauer. Reproduction at advanced maternal age. Fertil Steril 2015.

Complicanze gravidiche in relazione all'età

Sauer, 2015

SE IN UN PRIMO TEMPO

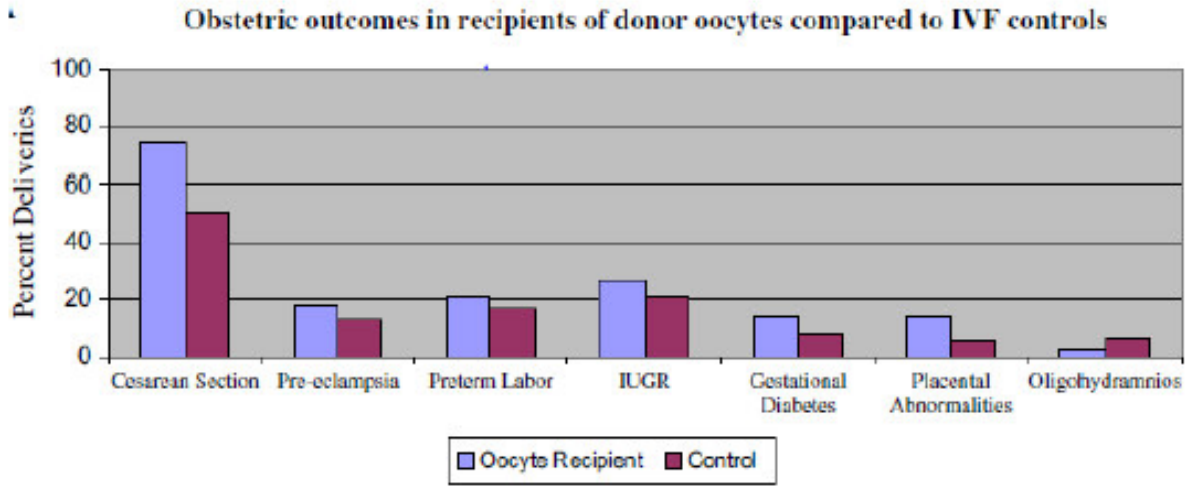
Obstetric outcomes in donor oocyte pregnancies compared with advanced maternal age in in vitro fertilization pregnancies

Sacha A. Krieg, M.D., Ph.D.,[a] Melinda B. Henne, M.D., M.S.,[b] and Lynn M. Westphal, M.D.[c]

Fertility and Sterility® Vol. 90, No. 1, July 2008

IVF with donated oocytes
may *not* be at increased risk of obstetric complications
when compared with women of **similar age** undergoing
IVF with autologous oocytes.

COMPLICATIONS related
ADVANCED MATERNAL AGE



….APPARE INVECE DAI DATI DELLA LETTERATURA CHE L'AUMENTATO RISCHIO OSTETRICO NELLE GRAVIDANZE OTTENUTE CON OVODONAZIONE NON SIA LEGATO ALL'ETA' MATERNA MA ALL'OVODONAZIONE STESSA

DOI: 10.1111/1471-0528.14257
www.bjog.org

Systematic review

Obstetric and neonatal complications in pregnancies conceived after oocyte donation: a systematic review and meta-analysis

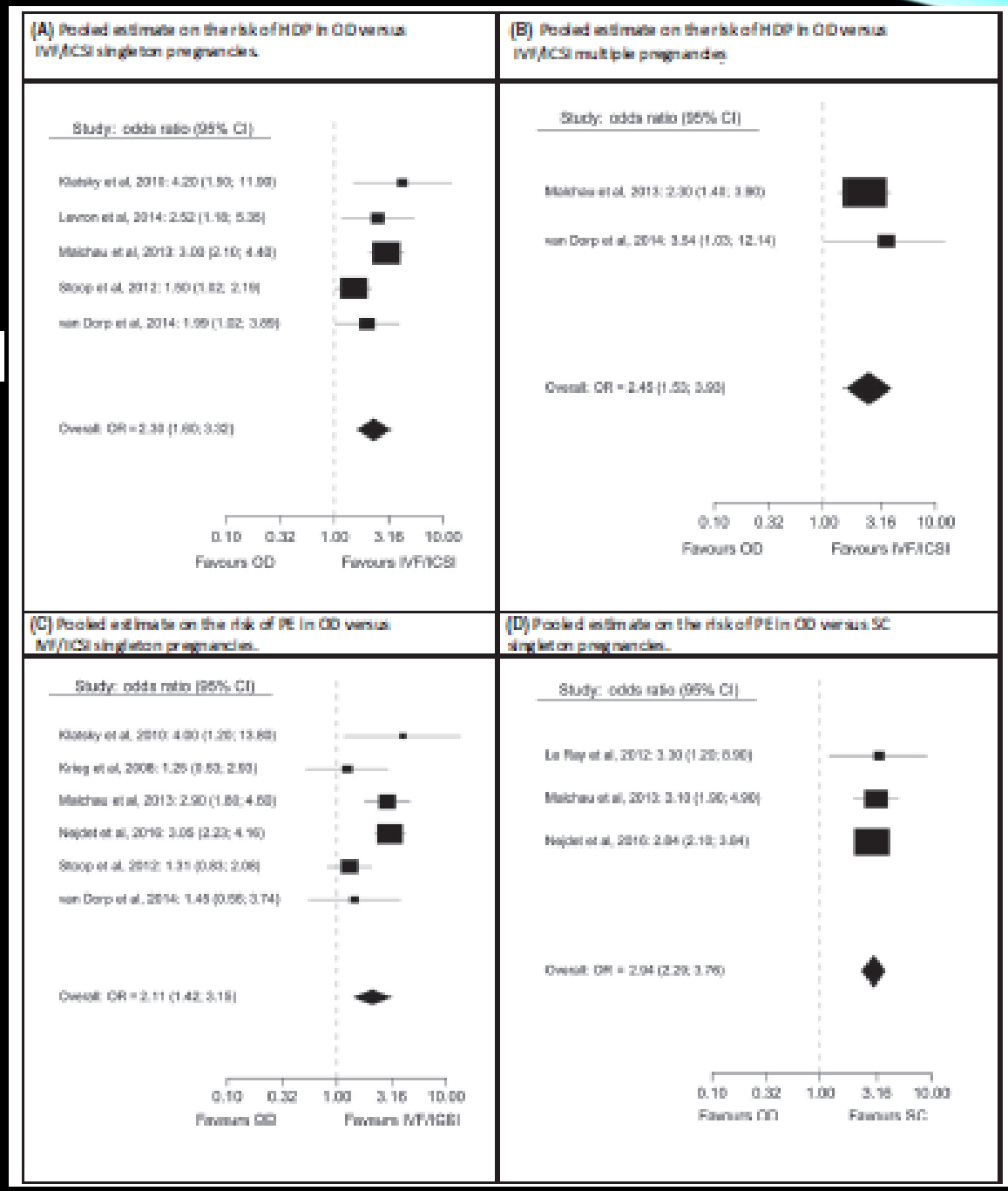
M Storgaard,[a] A Loft,[b] C Bergh,[c] UB Wennerholm,[d] V Söderström-Anttila,[e] LB Romundstad,[f,g] K Aittomaki,[h] N Oldereid,[i] J Forman,[j] A Pinborg[k]

Please cite this paper as: Storgaard M, Loft A, Bergh C, Wennerholm UB, Söderström-Anttila V, Romundstad LB, Aittomaki K, Oldereid N, Forman J, Pinborg A. Obstetric and neonatal complications in pregnancies conceived after oocyte donation: a systematic review and meta-analysis. BJOG 2017;124:561–572.

There is moderate-quality evidence that the risk of HDP is higher in OD singleton and multiple pregnancies than in IVF pregnancies (GRADE+++).

There is moderate-quality evidence that the risk of PE is higher in singleton and multiple OD pregnancies than in IVF pregnancies and SC pregnancies (GRADE+++).

There is moderate-quality evidence that the risk of CS is higher in singleton OD than in singleton IVF and SC pregnancies (GRADE+++).



Le evidenze sono di moderata qualità per la maggior incidenza di taglio cesareo di parto pretermine e di basso peso alla nascita e SGA nelle gravidanze singole e multiple ottenute con ovodonazione rispetto alle gravidanze da PMA omologa o spontanee. Evidenza di scarsa qualità per il rischio aumentato di emorragia postpartum. Nessun aumento di rischio per l'incidenza di diabete gestazionale.

Discussion

Main findings

Our meta-analyses showed that the risk of HDP, PE, LBW, PTB and CS was higher in OD than in IVF singleton pregnancies. For OD versus SC singleton pregnancies the risk of PE, PTB, LBW and CS was increased, and for OD versus IVF multiple pregnancies the risk of HDP and PE was increased. The AORs ranged from 1.55 to 3.31, the highest comparative risk being that of PE in OD versus PE in IVF multiple pregnancies and the lowest comparative risk being that of LBW in OD versus LBW in IVF singleton pregnancies. The prevalence of SGA was similar in OD versus IVF and SC singleton infants and also in OD versus IVF multiple infants.

Further meta-analyses showed that the risk of postpartum haemorrhage in singleton pregnancies was higher after OD than after IVF, while there was no statistically significant difference in the prevalence of gestational diabetes mellitus.

It has been hypothesised that the abnormal placental development in HDP pregnancies is caused by the genetically unknown fetus that induces immunological reactions in the oocyte recipients.[34,37,38] This is confirmed by the fact that studies on histological and immuno-histochemical abnormalities in human placentae have shown that signs of placental pathology such as villitis, chronic deciduitis, maternal-floor infarction and ischaemic changes are more likely to occur in OD than in IVF pregnancies.[39,40]

In has been suggested that human leukocy
(HLA) matching of oocyte donors and their reci
hinder the immunologic mismatch between n
fetus, thus lowering the risk of placental patl
HDP.[40] This is supported by a recent finding o
cantly higher level of HLA matching between n
child than would be expected by chance in
uncomplicated OD pregnancies with unrelated do

Conclusions

This review and meta-analysis show elevated risks of HDP, PE, LBW, PTB, CS and postpartum haemorrhage in OD versus IVF and SC pregnancies, while there was no difference in the incidence of SGA and gestational diabetes mellitus.

The increased risks of adverse maternal and neonatal outcomes should be taken into account when offering parental counselling prior to fertility treatment with OD and when planning ante- and perinatal care.

Since some of the risks in OD pregnancies such as HDP and postpartum bleeding are further increased in multiple pregnancies, single-embryo transfer should be recommended, and couples wishing for a multiple pregnancy should be properly informed about their risk profile prior to double-embryo transfer.

There is high-quality evidence from meta-analyses that the incidence of PE is reduced by at least 10% when administering 60–150 mg aspirin daily after the first trimester of pregnancy to women at increased risk of developing PE.[42–45] It has been speculated that aspirin adjusts an imbalance in the thromboxane A_2/prostacyclin ratio that is

associated with increased vasoreactivity, which is part of
the pathology in pre-eclamptic pregnancies. In the UK
National Institute for Health and Clinical Excellence
(NICE) guidelines it is recommended that aspirin should
be administered to women with one high-risk factor for
PE, such as chronic hypertension or pregestational diabetes
mellitus, or two or more moderate-risk factors for PE, such
as first pregnancy or/and age >40.[44] Meanwhile, oocyte
donation is not listed among the risk factors in the NICE
guideline. Since OD increases the risk for PE by about two
to three times compared to SC and even more than some
of the other risk factors mentioned in the NICE guideline,
prophylactic low-dose aspirin treatment should be consid-
ered for OD pregnancies.

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www.bjog.org

Systematic review

Donor oocyte conception and pregnancy complications: a systematic review and meta-analysis

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Hypertensive disorders in DO pregnancy

Pregnancy-induced hypertension and singleton DO pregnancy

Study or Subgroup	Donor Oocyte IVF Events	Total	Autologous Oocyte IVF Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lewron 2014	22	139	7	126	15.2%	3.20 [1.32, 7.77]
Malchau 2013	34	215	492	9833	43.7%	3.57 [2.45, 5.20]
Soderstrom-Anttila 1998	12	41	8	68	10.5%	3.10 [1.14, 8.42]
Stoop 2012	25	147	13	147	26.6%	2.11 [1.03, 4.31]
Wiggins and Main 2005	6	35	2	37	4.0%	3.62 [0.69, 19.02]
Total (95% CI)		577		10211	100.0%	3.08 [2.26, 4.19]
Total events	99		522			

Heterogeneity: Chi² = 1.70, df = 4 (P = 0.79); I² = 0%
Test for overall effect: Z = 7.15 (P < 0.00001)

Odds Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Risk in Autologous IVF Risk in DO IVF

Pre-eclampsia and singleton DO pregnancy

Study or Subgroup	DO IVF Pregnancy Events	Total	Autologous IVF pregnancy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dviri 2012	17	105	3	87	9.9%	5.41 [1.53, 19.13]
Lewron 2014	13	139	6	126	20.5%	2.06 [0.76, 5.60]
Malchau 2013	21	215	316	9833	43.6%	3.26 [2.05, 5.18]
Stoop 2012	15	147	8	147	25.8%	1.97 [0.81, 4.81]
Total (95% CI)		606		10193	100.0%	2.90 [1.98, 4.24]
Total events	66		333			

Heterogeneity: Chi² = 2.34, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 5.45 (P < 0.00001)

Odds Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Risk in Autologous IVF Risk in DO IVF

Hypertensive disorders in pregnancy with maternal age > 40 years

Study or Subgroup	Donor Oocyte IVF Events	Total	Autologous Oocyte IVF Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Keegan 2007	20	102	17	156	92.5%	1.99 [0.99, 4.02]
Wiggins and Main 2005	10	27	1	12	7.5%	6.47 [0.72, 57.88]
Total (95% CI)		129		168	100.0%	2.33 [1.21, 4.49]
Total events	30		18			

Heterogeneity: Chi² = 1.02, df = 1 (P = 0.31); I² = 2%
Test for overall effect: Z = 2.52 (P = 0.01)

Odds Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Risk in Autologous Risk in DO

Figure 3. Primary outcome – subgroup analysis.

Main findings

The results of the meta-analysis described above show that the risk of developing hypertensive disorders in pregnancy is significantly higher with DO pregnancy when compared with autologous IVF pregnancy. The studies included singletons as well as twins; therefore, we studied the effect in singleton and multiple pregnancies separately. The increased risk was found in all subgroups, including women of advanced maternal age. When the risk of hypertensive disorders in pregnancy was subdivided into two groups, PIH and PET, the risk of both complications was higher in DO pregnancies. These findings are consistent with some previous observational studies.[8–12,29,30] Multiple pregnancy is a known risk factor for developing hypertensive disorders; however, our analysis suggested that DO pregnancy is independent of multiple pregnancies for the development of hypertensive disorders. The risks of SGA and preterm delivery are significantly higher in DO pregnancy. Our meta-analysis showed that the chances of caesarean delivery for singletons are significantly higher with DO pregnancy. Similar findings are reported by other authors.[3,9,10,12]

Although the DO technique proved to be an excellent treatment option for many women to achieve pregnancy, it exposes them to higher risks of many maternal complications, including maternal death.[50–52] Women undergoing DO conception should be counselled before conception about the increased risks during DO pregnancy, and that the risk is independent of age or multiple pregnancies.[51,52] Obstetricians should be aware of the increased pregnancy risks in this particular group of patients, and appropriate surveillance strategies should be in place during antenatal, intrapartum, and postnatal care.[51] The use of serial growth scans to diagnose SGA has resource implications. Therefore, an individualised surveillance and management strategy should be considered. The use of low-dose aspirin in DO pregnancy in the absence of any other risk factors requires further evaluation. Oocyte cryopreservation for future fertility is suggested as an alternative for avoiding DO in selected cases;[34] however, data on success rates, the effect on continuing pregnancy, and adverse effects are limited.[53]

Conclusion

In the light of current evidence, DO pregnancy should be considered as an independent risk factor for pregnancy complications, including hypertensive disorders of pregnancy, SGA, preterm delivery, and caesarean section. Women should be counselled carefully about these risks before undergoing DO-assisted conception. These women should be managed in high-risk obstetric clinics with individualised monitoring and management strategies to reduce complications. The role of low-dose aspirin in DO pregnancy in the absence of any other risk factors requires further research. The use of serial growth scans in DO pregnancies needs further evaluation. Limited evidence attributed these complications to immunological origin; further research is required to explain the pathogenesis involved in donor oocyte pregnancies.

In DO pregnancies the fetus is allogeneic to the gestational carrier.
Therefore, the mother has to cope with a higher degree of antigenic dissimilarity compared with spontaneously conceived pregnancies.
Increased immunological activity
and fibrinoid deposition was noted at the maternal–fetal interface in DO pregnancies
This represents a host versus graft rejection-like phenomenon.

Gestational hypertension and donor eggs: elusive yet dangerous

MV Sauer

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Linked article: This is a mini commentary on YB Jeve et al., pp. 1471–1480 in this issue. To view this article visit http://dx.doi.org/10.1111/1471-0528.13910.

Published Online 10 March 2016.

Egg and embryo donation has been used for over 30 years to address female infertility. It has evolved into mainstream practice following a series of empiric clinical studies, each demonstrating surprisingly favourable results when applied to a wide variety of challenging patients (Sauer *Reprod Biomed Online* 2006;12:153–62). The broad appeal of egg donation relates to reversing the natural age-related decline in the fertility of older patients, and its use allows women to bear children beyond menopause.

Consistently, gestational hypertension has occurred at higher than anticipated rates among recipients (Pados *Hum Reprod* 1994;9:538–42). These observations were particularly striking because efforts to pre-screen women for health prior to pregnancy were rigorously applied. Most worrisome was the accelerated and often severe pre-eclampsia that developed among patients with an underlying hypertensive profile. Placentas often demonstrated abnormalities at the fetal–maternal interface. Pronounced villitis noted in histologic sections suggest an exaggerated immune-mediated response that might be secondary to antigenic dissimilarity between fetus and mother. Likewise, babies were frequently found to be small for gestational age and stillbirths were noted in several patients near term, usually accompanied by hypertension. All of these risks are exaggerated when recipients are older, as they often are, with many individuals being over 50 years of age (Kort *Am J Perinatol* 2012;29:245–250).

The value of meta-analysis lies in the ability to combine results from cohort and case series comparisons to increase the power and reliability of otherwise empiric findings. The results indicate that recipients of donor eggs, independent of age, are at high risk for gestational hypertensive disorders. Yet, there are few, if any, reliable tests of cardiovascular reserve that predict which patients will be affected, and among the affected, which will be the most severely impaired.

It is relatively common to see the phrases 'counselled carefully' when referring to prospective recipients of donor eggs. I believe this is much easier said than done. Denial is great in all patients, particularly women intent on having children. Most have never suffered a severe life-threatening illness and do not recognise the risks of pregnancy (Sauer *Fertil Steril* 2015;103:1136–43). I have been impressed that couples actually return to try again after losing a baby to stillbirth or severe prematurity in the setting of hypertensive disease. Rarely are they dissuaded from another attempt at pregnancy, despite the warnings and armed with first-hand knowledge of the high-risk nature of their circumstance. Often the disease strikes again in the subsequent pregnancy, jeopardising both the life of the mother and the life of the unborn.

Evidence-based results aid clinicians in leveraging some of the enthusiasm of older patients seeking to become parents through egg donation against the hard biological realities of childbearing, which is inherently high risk at advanced reproductive age. It is a necessary part of true *informed* consent to alert recipients to all potential dangers.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information. ■

…E ANCORA

- Am J Obstet Gynecol. 2014 Oct;211(4):383.e1-5. doi: 10.1016/j.ajog.2014.03.044. Epub 2014 Mar 19.

- **The 'immunologic theory' of preeclampsia revisited: a lesson from donor oocyte gestations.**

- Levron Y1, Dviri M1, Segol I1, Yerushalmi GM1, Hourvitz A1, Orvieto R1, Mazaki-Tovi S1, Yinon Y1.
- Department of Obstetrics and Gynecology, Sheba Medical Center, Tel-Hashomer, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.

- **Abstract**

- **OBJECTIVE:** To determine the prevalence of placental complications in patients conceived through donor versus autologous oocytes.
- **STUDY DESIGN:** A retrospective cohort study including 2 groups of patients who conceived through in vitro fertilization using: (1) donor oocyte (n = 139) and (2) autologous oocyte (n = 126). Only singleton gestations were included. The rate of placental complications including preeclampsia, gestational hypertension, and intrauterine growth restriction was compared between these 2 groups.
- **RESULTS:** The women who conceived using donor oocytes were older compared with women who conceived using autologous oocytes (median maternal age 45 vs 41, P < .01). The rate of hypertensive diseases of pregnancy including gestational hypertension and preeclampsia was significantly higher in ovum donor recipients compared with women conceived with autologous oocytes (25% vs 10%, P < .01). Similarly, the rate of intrauterine growth restriction was also higher among patients conceived through oocyte donation although it did not reach statistical significance (9.3% vs 4%, P = .08). When maternal age was restricted to ≤45 years, the rate of hypertensive diseases of pregnancy remained significantly higher among ovum donor compared with autologous oocyte recipients (22% vs 10%, P = .02). Adjustment for maternal age, gravidity, parity, and chronic hypertension revealed that oocyte donation was independently associated with higher rate of hypertensive diseases of pregnancy (P = .01).
- **CONCLUSION:** Patients conceived through oocyte donation have an increased risk for placental complications of pregnancy. These findings support the 'immunologic theory' suggesting that immunologic intolerance between the mother and the fetus may play an important role in the pathogenesis of preeclampsia.

AM J OBSTET GYNECOL. 2016 MAR;214(3):328-39.
DOI:10.1016/J.AJOG.2015.11.020. EPUB 2015 NOV 25.

OOCYTE DONATION PREGNANCIES AND THE RISK OF PREECLAMPSIA OR GESTATIONAL HYPERTENSION: A SYSTEMATIC REVIEW AND METAANALYSIS.

MASOUDIAN P1, NASR A2, DE NANASSY J1, FUNG-KEE-FUNG K3, BAINBRIDGE SA4, EL DEMELLAWY D5.

ABSTRACT

- The purpose of this study was to determine whether pregnancies that were achieved via oocyte donation, compared with pregnancies achieved via other assisted reproductive technology methods or natural conception, demonstrate increased risk of preeclampsia or gestational hypertension. Comparative studies of pregnancies that were achieved with oocyte donation vs other methods of assisted reproductive technology or natural conception with preeclampsia or gestational hypertension were included as 1 of the measured outcomes. Abstracts and unpublished studies were excluded. Two reviewers independently selected studies, which were assessed for quality with the use of methodological index for non-randomized studies, and extracted the data. Statistical analysis was conducted. Of the 523 studies that were reviewed initially, 19 comparative studies met the predefined inclusion and exclusion criteria and were included in the metaanalysis, which allowed for analysis of a total of 86,515 pregnancies. Our pooled data demonstrated that the risk of preeclampsia is higher in oocyte-donation pregnancies compared with other methods of assisted reproductive technology (odds ratio, 2.54; 95% confidence interval, 1.98-3.24; P < .0001) or natural conception (odds ratio, 4.34; 95% confidence interval, 3.10-6.06; P < .0001). The risk of gestational hypertension was also increased significantly in oocyte donation pregnancies in comparison with other methods of assisted reproductive technology (odds ratio, 3.00; 95% confidence interval, 2.44-3.70; P < .0001) or natural conception (odds ratio, 7.94; 95% confidence interval, 1.73-36.36; P = .008). Subgroup analysis that was conducted for singleton and multiple gestations demonstrated a similar risk for preeclampsia and gestational hypertension in both singleton and multiple gestations. This metaanalysis provides further evidence that supports that egg donation increases the risk of preeclampsia and gestational hypertension compared with other assisted reproductive technology methods or natural conception.

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ORIGINAL ARTICLE
THIEME MEDICAL PUBLISHERS 333 SEVENTH AVENUE, NEW YORK, NY 10001, USA.

THE IMPACT OF SPERM AND EGG DONATION ON THE RISK OF PREGNANCY COMPLICATIONS

MICHAL FISHEL BARTAL, BAHA M. SIBAI, YOSSI BART, AVI SHINA, SHALI MAZAKI-TOVI, ISRAEL HENDLER MICHA BAUM *EYAL SCHIFF

- **Abstract**
- Objective The aim of this study was to evaluate obstetric outcomes in relation to the extent of donor sperm exposure with and without egg donation.
- Materials and Methods This is a retrospective cohort study in a single tertiary care center. All women with a singleton pregnancy who conceived following sperm donation (SD) were included. Obstetrics and neonatal outcomes for pregnancies following single SD were compared with pregnancies following repeat SD from the same donor. In a secondary analysis, we compared pregnancy outcomes among three modes of assisted reproductive technology (intrauterine insemination [IUI-SD], in vitro fertilization [IVF-SD], and IVF sperm + egg donation [IVF-SD + ED]).
- Results A total of 706 pregnant women met the inclusion criteria, 243 (34.4%) following the first SD and 463 (65.6%) following repeat donations. Compared with repeat SDs, single donation was not associated with higher rates of preterm delivery (12.8 vs. 12.7%, respectively, p = 0.99), preeclampsia (7.0 vs. 6.9%, p = 0.999), and intrauterine growth restriction (4.1 vs. 3.9%, p = 0.88). Pregnancies following IVF-SD + ED had increased risk for preeclampsia (adjusted odds ratio [AOR], 3.1; 95% confidence interval [CI], 1.5–6.6), preterm labor (AOR, 2.4; 95% CI, 1.1–5.4), and cesarean section (AOR, 2.1; 95% CI, 1.0–4.3) compared with IUI-SD and IVF-SD.
- Conclusion The extent of donor sperm exposure did not correlate with obstetrics complications, but double gamete donation was associated with increased risk for preeclampsia, preterm labor, and cesarean section.

Human Reproduction Update, Vol.16, No.6 pp. 704–712, 2010
Advanced Access publication on June 12, 2010 doi:10.1093/humupd/dmq017

human reproduction update

Clinical and immunologic aspects of egg donation pregnancies: a systematic review

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Maternal complications

ED enables women of advanced age to achieve successful pregnancies. However, advanced maternal age leads to potential medical and obstetric complications. Pregnant recipients above the age of 40 years are at an increased risk for gestational diabetes, pre-eclampsia and thrombophlebitis (Michalas *et al.*, 1996); above the age of 45 years they are at an increased risk of hypertension, proteinuria, premature rupture of membranes, second- and third trimester haemorrhage, preterm delivery and lower mean infant birthweights (Soares *et al.*, 2005; Simchen *et al.*, 2006). One study that corrected for maternal age and multiple gestation concluded that women who conceived with donor oocytes remain at high risk for preterm labour, pre-edampsia and protracted labour, requiring Caesarean section delivery (Henne *et al.*, 2007). The rate of Caesarean section deliveries in ED pregnancies is increased compared with spontaneous conceptions, and is reported to range from 40 to 76% of cases (Blanchette, 1993; Sauer *et al.*, 1996; Abdalla *et al.*, 1998; Soderstrom-Anttila *et al.*, 1998a, b; Yaron *et al.*, 1998; Kavic and Sauer, 2001; Klein and Sauer, 2002; Sheffer-Mimouni *et al.*, 2002).

Pregnancy-induced hypertension

ED pregnancies are associated with a higher than expected incidence of pregnancy-induced hypertension (PIH), ranging from 16 to 40% of cases (Serhal and Craft, 1989; Blanchette, 1993; Abdalla *et al.*, 1998;

increased rate of hypertension in ED pregnancies is related to advanced maternal age, nulliparity and ovarian failure (Pados *et al.*, 1994), since these factors are associated with multiple obstetric complications (Krieg *et al.*, 2008). However, a study by Sheffer-Mimouni *et al.* (2002) found that these factors were not independent risk factors for PIH and they concluded that the higher incidence of PIH in ED pregnancies is a result of an altered immune response. In another report, an increased risk for PIH was observed in women with ED pregnancies in women <35 years or >40 years of age (Keegan *et al.*, 2007).

These data suggest that PIH is more frequent when ED involves an immunologically unrelated donor.

Discussion

Although ED gives infertile women the opportunity to conceive, it may lead to harmful consequences during pregnancy if compared with spontaneously conceived pregnancies. This review gave an overview of the consequences of ED pregnancies with respect to their atypical fetal-maternal immunologic relationships. Review of the literature showed that women who conceived by ED have an increased risk of PIH (Serhal and Craft, 1989; Blanchette, 1993; Abdalla *et al.*, 1998; Soderstrom-Anttila *et al.*, 1998a, b; Salha *et al.*, 1999; Sauer, 2001; Klein and Sauer, 2002; Sheffer-Mimouni *et al.*, 2002; Wiggins and Main, 2005; Keegan *et al.*, 2007), an increased rate of Caesarean section deliveries (Blanchette, 1993; Sauer *et al.*, 1996; Abdalla *et al.*, 1998; Soderstrom-Anttila *et al.*, 1998a, b; Yaron *et al.*, 1998; Kavic and Sauer, 2001; Klein and Sauer, 2002; Sheffer-Mimouni *et al.*, 2002), an increased risk of post-partum haemorrhage (Sheffer-Mimouni *et al.*, 2002), and an increased risk of first trimester vaginal bleeding (Pados *et al.*, 1994; Abdalla *et al.*, 1998; Soderstrom-Anttila *et al.*, 1998a, b). All of these complications can be the consequence of ED pregnancies; however, other factors that correlate with infertility and age could also be an underlying cause. For example, women

Although the literature conclusively demonstrates an increased risk of ED-related pregnancy complications for the mother, it does not show an increased complication rate for the fetus or newborn

Conclusions

ED provides a valuable addition to the list of treatment options for women who require ART. The benefits of having a take-home baby are counter-balanced by the higher risk of maternal morbidity. The increased rate of complications may be related to the allogeneic nature of the fetus. To understand the underlying mechanism(s) of acceptance of the allogeneic fetus, more research regarding the unique immunologic aspects of ED pregnancies is warranted. Understanding the role of the immune system in successful ED pregnancies also has broader biomedical significance in that it may also give insight into immune mechanisms leading to immunologic tolerance for HLA mismatched solid organ transplants.

LA TEORIA IMMUNOLOGICA

Placental pathology

At the fetal–maternal interface significant histological and immunohistochemical differences are present when comparing ED and non-donor IVF pregnancies. Characteristic pathologic findings in ED cases include a higher incidence of villitis of unknown etiology, chronic deciduitis, massive chronic intervillositis, maternal floor infarction and ischemic changes, as seen with pre-eclampsia (Styer *et al.*, 2003; Perni *et al.*, 2005; Gundogan *et al.*, 2009) (Fig. 2). The chronic deciduitis observed in ED placentas is characterized by its severity and the presence of a dense, fibrinoid deposition in the basal plate. Furthermore, an increased infiltration of CD4+ T-helper cells and CD56+ natural killer (NK) cells is present in the basal plate of ED placentas (Gundogan *et al.*, 2009). It is in the basal plate where extravillous trophoblast (of fetal origin) interfaces with and invades the maternal tissue. The extravillous trophoblast cells do not express classical HLA-A and HLA-B molecules, thereby preventing interaction with cytotoxic T cells. However, they do express a unique combination of HLA antigens (HLA-C and the non-classical HLA-E and HLA-G) that interact with KIR receptors on uterine NK cells (Hiby *et al.*, 2004; Dietl *et al.*, 2006; Sargent *et al.*, 2006), although HLA-C can also serve as a target molecule for CD8+ T-cells (Tilburgs *et al.*, 2009a, b). The striking findings of a dense fibroid deposition and mononuclear cell infiltration in the basal plate suggest that the placental abnormalities are related to an immune-mediated response that is more pronounced in ED pregnancies. The placental damage may be the consequence of a type of graft-versus-host disease and/or organ rejection type of reaction (Gundogan *et al.*, 2009).

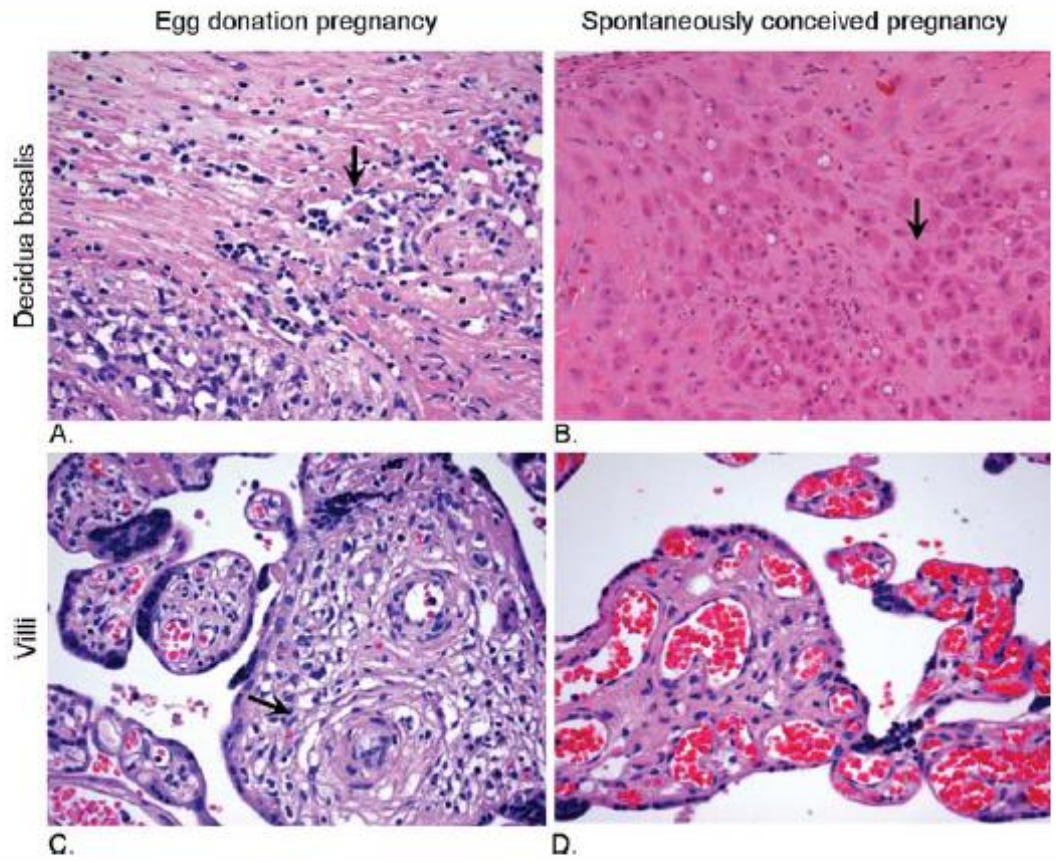

Figure 2 Photomicroscopic images of placentas from ED and spontaneously conceived pregnancies. (Sections stained with hematoxylin and eosin, all original magnification ×400.) (**A**) Decidua basalis of ED pregnancy placenta with deciduitis illustrated by the infiltration of mononuclear cells (arrow). (**B**) Normal decidua basalis from a spontaneously conceived pregnancy with normal decidual cells (arrow). (**C**) Villi from an ED pregnancy placenta. The stromal cellularity is increased by an infiltrate of mononuclear cells (arrow). (**D**) Villi of a spontaneously conceived pregnancy placenta.

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human reproduction update

Clinical and immunologic aspects of egg donation pregnancies: a systematic review

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Una gravidanza « di successo» è un paradosso immunologico: il feto presenta geni materni e geni paterni, ma non è rigettato dal sistema immunitario della madre, per un periodo di 9 mesi.
Sin da quando i tessuti fetali vengono in contatto con il sangue materno, si mettono in atto dei meccanismi che consentono una tolleranza immunitaria, altrimenti il prodotto del concepimento sarebbe attaccato sia dal sistema immunitario innato che acquisito.
Nelle gravidanze spontanee si crea un'interfaccia materno – fetale che consente al feto- semiallogenico di non essere rigettato, vi è una predominanza della risposta immune T-helper 2, ed una attivazione di cellule T «REGOLATORIE» che mantiene il sistema immunitario materno in uno stato di tolleranza immunitaria che consente al feto di sopravvivere nell'utero.

Parallels with blood transfusions

The mechanism(s) involved in the effective down-regulation of the maternal immune response to the semi-allogeneic fetus can be compared with the ones involved in the development of tolerance by pre-transplant blood transfusions. Blood transfusions have an immunomodulating effect, as demonstrated by the positive association of kidney graft survival and the number of allogeneic transfusions (Opelz *et al.*, 1973). In addition, a beneficial effect of HLA-DR matched transfusions has been shown in kidney (Lagaaij *et al.*, 1989) and heart (van der Mast and Balk, 1997) transplantation. Furthermore, more HLA alloantibodies are formed after HLA mismatched transfusions compared with HLA-DR shared transfusions (Bayle *et al.*, 1995). Down-regulation of the immune response may occur by the induction of regulatory CD4+ T-cells, which are induced when the donor and recipient share at least one HLA-class II molecule (Claas *et al.*, 2001). This immunomodulating effect only occurs in the case of blood transfusions which are semi-allogeneic or involve one shared HLA-DR. Blood transfusions that are fully HLA mismatched with the recipient lead to immunization, rather than tolerance of the patient.

et al., 2003). The currently accepted view is that a successful pregnancy depends on an appropriate balance of the different components of the maternal immune system, with predominance of T helper 2 immunity (Wegmann *et al.*, 1993; Saito *et al.*, 1999, 2007; Saito and Sakai, 2003). At the human fetal–maternal interface, maternal recognition of fetal antigens presented by trophoblast cells or by fetal cells trafficking into the maternal circulation is essential for the induction of immunoregulatory mechanisms (Sindram-Trujillo *et al.*, 2003). It is

apparent that activated T cells at the maternal interface include regulatory T cells (Sindram-Trujillo *et al.*, 2003; Tilburgs *et al.*, 2006). These regulatory T cells have an important role in the local down-regulation of human fetal-specific allogeneic T cell responses (Tilburgs *et al.*, 2008). All of these protective mechanisms maintain the immunosuppressive environment in the pregnant uterus, and in this way the semi-allogeneic fetus is capable of surviving in the uterus.

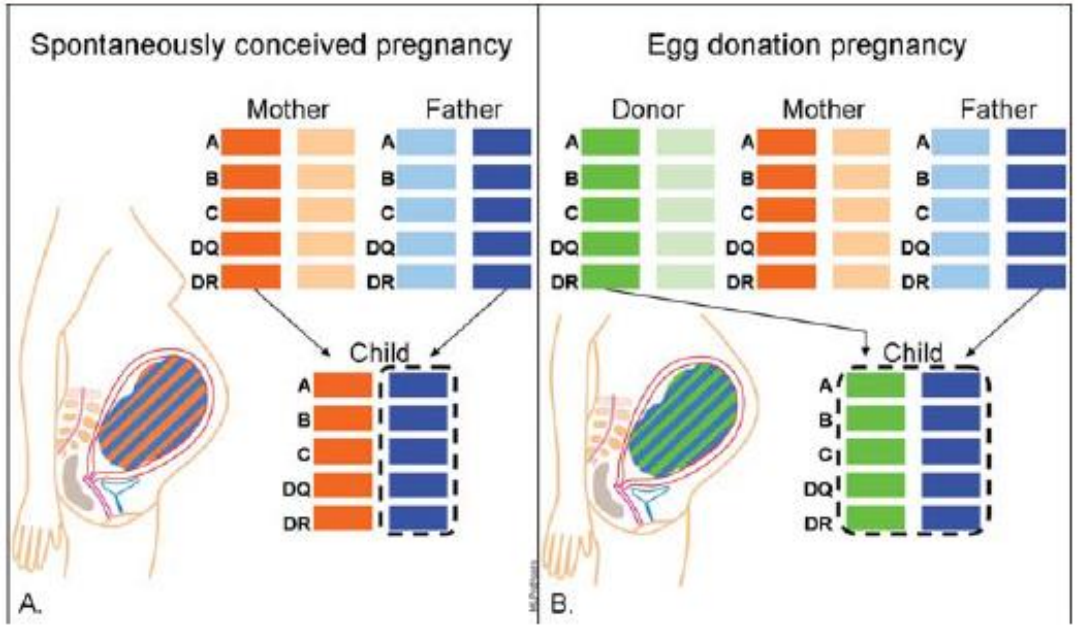

Figure 3 Schematic of the inheritance of the most immunogenic HLA-antigens in a spontaneously conceived and an ED pregnancy. (**A**) In a spontaneously conceived (or non-donor IVF) pregnancy the child inherits antigens of the father and antigens of the mother. The five most immunogenic HLA antigens (HLA-A, -B, -C, -DR and -DQ) are depicted in orange for the mother and in blue for the father. The child inherits one set from the mother and one set from the father. Comparing the antigens of the child with the mother a maximum of five mismatches is possible (dashed line). (**B**) In an ED pregnancy involving an unrelated donor, no antigens from the mother are present in the fetus. The antigens of the donor are depicted in green and the antigens from the father in blue. The set of genes inherited by the child contains no antigens of the mother, therefore, a maximum of 10 mismatches is possible between the mother and the child in an ED pregnancy (dashed line).

Immune studies in ED

Although other mechanisms can be involved, it is likely that down-regulation of the maternal alloimmune response to the fetus in an ED pregnancy is far more difficult than in spontaneously conceived pregnancies with semi-allogeneic fetuses. Compared with spontaneously conceived pregnancies, there is a higher degree of antigenic dissimilarity in ED cases. If the five most immunogenic HLA antigens (HLA-A, -B, -C, -DR and -DQ) are taken into consideration, the maximal number of mismatches in spontaneous conceived pregnancies would be 5. In ED pregnancies this could reach a maximum of 10 mismatches (Fig. 3). Since ED pregnancies are characterized by matches will become more apparent in ED pregnancies. In pregnant women who conceived by ED, an increased percentage of intracellular interferon-γ (Th1, also involved in spiral artery formation) and interleukin-4 (Th2)-positive CD4+ T-lymphocytes was found in peripheral blood compared with pregnant women after spontaneous conception (Chernyshov *et al.*, 2008). This hyperactivation of Th1 and Th2 cells, induced by the allogeneic fetus, is specific for ED pregnancies. This suggests that the additional mechanism of Th2 immunity in ED pregnancies helps contribute to a successful pregnancy, even with a completely allogeneic fetus. Although the Chernyshov *et al.* (2008) study investigated immune cells in the peripheral blood, the widely accepted view is that the active immune mechanisms take place at the fetal–maternal interface; therefore, it is possible that an effect will be even more prominent at this location. Recently, a significant correlation between the extent of HLA mismatches and the percentage of CD4+CD25dim activated T-cells in the decidua parietalis of uncomplicated pregnancies was described (Tilburgs *et al.*, 2009a, b).

The immune system clearly plays an important role in ED pregnancies. Unfortunately, there is a lack of information from the mother's perspective about the long-term effects of exposure to foreign cells and antigens in the recipient, since the usual clinical end-point is the chance of having a take-home baby. From the literature it is unknown at present whether, later in life, the consequences of having conceived using ED may be harmful or not. In addition, when investigating immunologic aspects of ED pregnancies it is important to analyse the underlying reason why ED was necessary. For example, it is accepted that premature ovarian failure is a heterogeneous disorder in which some of the idiopathic forms are based on abnormal self-recognition by the immune system (Hoek *et al.*, 1997). It is possible that the pre-existing immunologic mechanisms involved in premature ovarian failure may contribute to the immunologic differences between ED and spontaneously conceived pregnancies.

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Immunological Tolerance, Pregnancy, and Preeclampsia: The Roles of Semen Microbes and the Father†

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"In one of the last articles which he wrote, the late Professor F.J. Browne (1958) expressed the opinion that all the essential facts about pregnancy toxemia are now available and that all that is required to solve the problem is to fit them together in the right order, like the pieces of a jigsaw puzzle. (1)"

"It appears astonishing how little attention has been given in reproductive medicine to the maternal immune system over the last few decades. (2)"

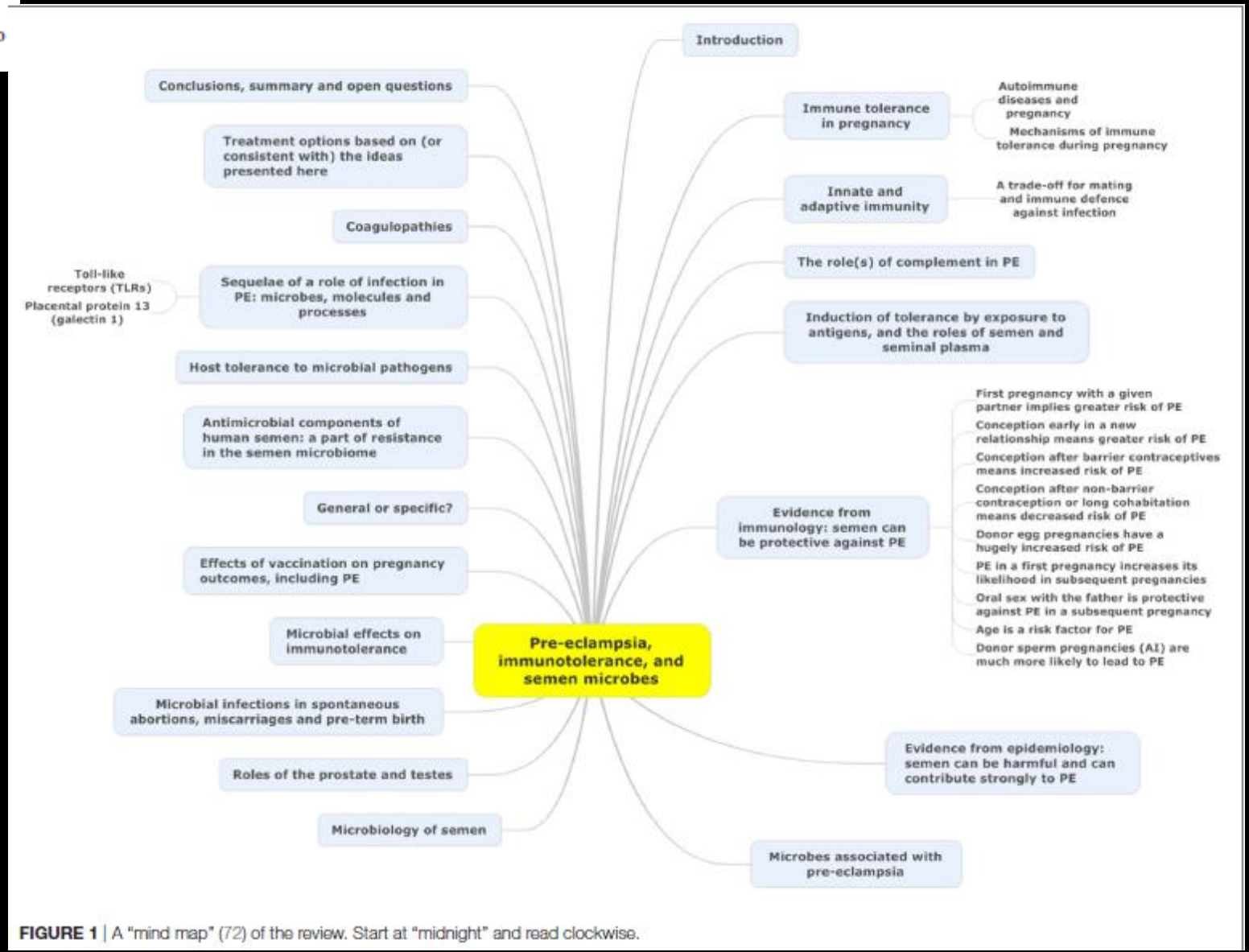

FIGURE 1 | A "mind map" (72) of the review. Start at "midnight" and read clockwise.

Review Article

Relationship between Maternal Immunological Response during Pregnancy and Onset of Preeclampsia

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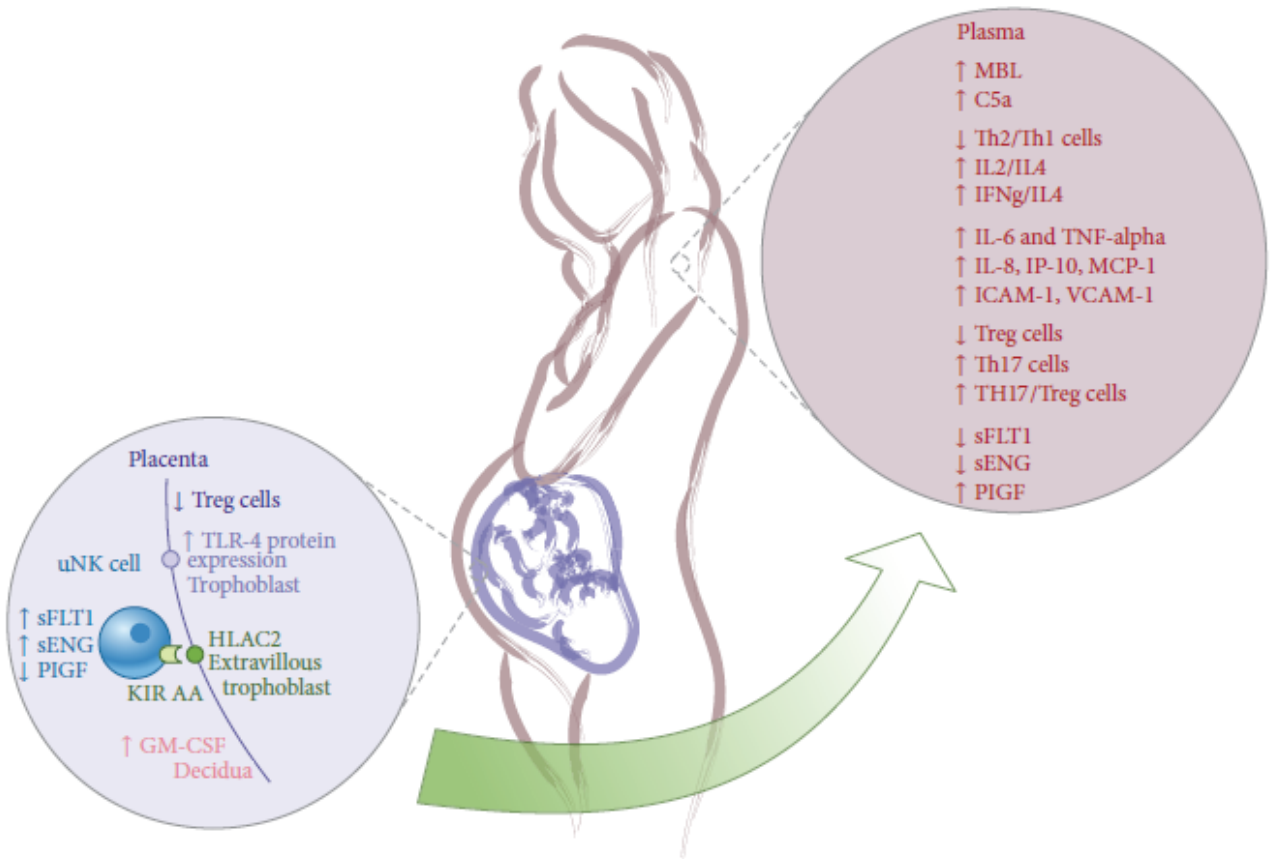

FIGURE 1: Maternofetal immune response in preeclampsia. A series of events occurs in the maternal-fetal interface in preeclampsia that result in an altered expression of different factors (PIGF, sENG, sFLT1, GM-CSF, and TLR-4) as compared to normal pregnancies. Similarly, the ratio among various populations of immune cells (Th17/Treg, Th1/Th2) differs from normality in preeclamptic patients. Regarding the complement system, preeclampsia enhances MBL and C5a synthesis. These changes are evidenced in peripheral blood in which the proinflammatory systemic environment is also seen with high IL-6 a, TNF-alpha, IL-8, IP-10, MCP-1, ICAM-1, and VCAM-1 levels. Treg: CD4+CD25+Foxp3+ T regulatory cells; TLR: toll-like receptor; HLA: the human leukocyte antigen; uNk cell: uterine natural killer cell; KIR: killer immunoglobulin-like receptor; sFLT1: soluble *fms-like* tyrosine kinase-1 factor; sENG: soluble endoglin; PIGF: placenta growth factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; MBL: mannose-binding lectin; Th cell: T helper cell; IL: interleukin; IFNg: interferon gamma; TNF-alpha: tumor necrosis factor alpha; IP-10: interferon-inducible-protein-10; MCP-1: monocyte chemotactic protein-1; ICAM-1: intercellular adhesion molecule 1; VCAM-1: vascular cell adhesion protein 1; Th17: a subpopulation of TCD4+ effector cells, Thelper 17 cells.

3. Maternal Tolerance in Pregnancy by Egg Donation

In ED pregnancies, the fetus is allogeneic to the mother. Fetal HLA arises from the donor's ovule and from the biological father of the future newborn child. In spontaneous pregnancies, has been an allogeneic trimester and pregnancy counterpart the pregnancy of the T-cells [

The larger number of mismatches in the five most immunogenic HLA antigens (HLA-A, -B, -C, -DR, and -DQ) in ED pregnancies may have clinical consequences. Indeed, the healthy uncomplicated term pregnancies containing a HLA-C mismatched child induce a higher percentage of $CD4+CD25^{dim}$ activated-T cells in decidua parietalis and contain functional $CD4+CD25^{bright}$ regulatory T-cells [

Although the literature describes higher maternal mortality in ED pregnancies (pregnancy-induced hypertension, preeclampsia, bleeding complications during the first trimester), a higher rate of complications (intrauterine growth restriction, congenital anomalies) for the fetus or newborn has not been demonstrated [4]. Nonetheless, ED pregnancies are more likely to end in preterm birth than pregnancies by autologous IVF (34% versus 19%) [98]. It is unknown in spontaneous preterm births that maternal anti-HLA class I seropositivity is significantly higher than in term births [114]. ED pregnancies (fetal allograft) may be associated with higher maternal anti-HLA I seropositivity than pregnancies by autologous IVF or those spontaneously conceived (fetal semi-allograft). Therefore, the higher levels of maternal anti-fetal HLA I antibodies in ED pregnancies may be the cause of the higher incidence of preterm birth in these pregnancies when compared with autologous IVF or spontaneous pregnancies. Typification of donors' and recipients' HLA to select haploidentical combinations can be considered in ED pregnancies in order to make them more immunologically comparable to spontaneous pregnancies.

A meta-analysis of retrospective gestational hypertension and preeclampsia was significantly higher in ED pregnancies than in pregnancies by autologous IVF (24.7% versus 7.4%, and 16.9% versus 4.9%, resp.,) [113].

BMJ Open

Relating the number of human leucocytes antigen mismatches to pregnancy complications in oocyte donation pregnancies: study protocol for a prospective multicentre cohort study (DONOR study)

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ABSTRACT

Introduction Oocyte donation (OD) enables women with reproductive failure to conceive. Compared with naturally conceived (NC) and in vitrofertilisation (IVF) pregnancies, OD pregnancies are associated with a higher risk of pregnancy complications. The allogeneic nature of the fetus in OD pregnancies possibly plays a role in the development of these complications. The objective of the current study is therefore to study the number and nature of human leucocyte antigen (HLA) mismatches between fetus and mother and its association with the development of hypertensive pregnancy complications.

Methods and analysis In this prospective multicentre cohort study, 200 patients visiting one of the 11 participating fertility centres in the Netherlands to perform OD or embryo donation or surrogacy will be invited to participate. These patients will be included as the exposed group. In addition, 146 patients with a NC pregnancy and 146 patients who applied for non-donor IVF are included as non-exposed subjects. These groups are frequency matched on age and ethnicity and only singleton pregnancies will be included. The primary clinical outcome of the study is the development of hypertensive disease during pregnancy. Secondary outcomes are the severity of the pre-eclampsia, time to development of pre-eclampsia and development of other pregnancy complications. The association of high number of HLA mismatches (>5) between mother and fetus will be determined and related to clinical outcome and pregnancy complication.

Ethics and dissemination This study received ethical approval from the medical ethics committee in the Leiden University Medical Centre, the Netherlands (P16.048, ABR NL56308.058.16). Study findings will be presented at (inter) national conferences and published in peer-reviewed journals.

Expected results

- We expect to find a higher degree of pregnancy complications in OD pregnancies compared with IVF and NC pregnancies.
- We expect to find a higher number of HLA mismatches between mother and fetus in a pregnancy conceived through OD compared with IVF and NC pregnancies.
- We expect to find an association between the development of hypertensive pregnancy complications and a higher number of HLA mismatches.
- We expect to find a higher number of HLA mismatches between mother and fetus in women who conceived through OD with severe hypertensive complication, and that the development of the (severe) preeclampsia is at earlier gestational age.
- The results of this project may provide new strategies in increasing the chance of a successful OD pregnancy, for instance by defining the optimum number of HLA mismatches between donor and recipient before pregnancy. This would imply a possibility to HLA typing and matching of donors and recipients of oocytes, and extra medical care or use of specific medication during pregnancy to optimise the pregnancy outcome.
- The results of this project may lead to changes in guidelines and protocols considering OD pregnancies regarding an optimal number of HLA mismatches for OD pregnancies.

The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis

Stéphanie Roberge, PhD; Kypros Nicolaides, MD; Suzanne Demers, MD, MSc; Jon Hyett, MD; Nils Chaillet, PhD; Emmanuel Bujold, MD, MSc

BACKGROUND: Preeclampsia and fetal growth restriction are major causes of perinatal death and handicap in survivors. Randomized clinical trials have reported that the risk of preeclampsia, severe preeclampsia, and fetal growth restriction can be reduced by the prophylactic use of aspirin in high-risk women, but the appropriate dose of the drug to achieve this objective is not certain.

OBJECTIVE: We sought to estimate the impact of aspirin dosage on the prevention of preeclampsia, severe preeclampsia, and fetal growth restriction.

STUDY DESIGN: We performed a systematic review and meta-analysis of randomized controlled trials comparing the effect of daily aspirin or placebo (or no treatment) during pregnancy. We searched MEDLINE, Embase, Web of Science, and Cochrane Central Register of Controlled Trials up to December 2015, and study bibliographies were reviewed. Authors were contacted to obtain additional data when needed. Relative risks for preeclampsia, severe preeclampsia, and fetal growth restriction were calculated with 95% confidence intervals using random-effect models. Dose-response effect was evaluated using meta-regression and reported as adjusted R^2. Analyses were stratified according to gestational age at initiation of aspirin ($\leq$16 and >16 weeks) and repeated after exclusion of studies at high risk of biases.

RESULTS: In all, 45 randomized controlled trials included a total of 20,909 pregnant women randomized to between 50-150 mg of aspirin daily. When aspirin was initiated at $\leq$16 weeks, there was a significant reduction and a dose-response effect for the prevention of preeclampsia (relative risk, 0.57; 95% confidence interval, 0.43–0.75; $P < .001$; R^2, 44%; $P = .036$), severe preeclampsia (relative risk, 0.47; 95% confidence interval, 0.26–0.83; $P = .009$; R^2, 100%; $P = .008$), and fetal growth restriction (relative risk, 0.56; 95% confidence interval, 0.44–0.70; $P < .001$; R^2, 100%; $P = .044$) with higher dosages of aspirin being associated with greater reduction of the 3 outcomes. Similar results were observed after the exclusion of studies at high risk of biases. When aspirin was initiated at >16 weeks, there was a smaller reduction of preeclampsia (relative risk, 0.81; 95% confidence interval, 0.66–0.99; $P = .04$) without relationship with aspirin dosage (R^2, 0%; $P = .941$). Aspirin initiated at >16 weeks was not associated with a risk reduction or a dose-response effect for severe preeclampsia (relative risk, 0.85; 95% confidence interval, 0.64–1.14; $P = .28$; R^2, 0%; $P = .838$) and fetal growth restriction (relative risk, 0.95; 95% confidence interval, 0.86–1.05; $P = .34$; R^2, not available; $P = .563$).

CONCLUSION: Prevention of preeclampsia and fetal growth restriction using aspirin in early pregnancy is associated with a dose-response effect. Low-dose aspirin initiated at >16 weeks' gestation has a modest or no impact on the risk of preeclampsia, severe preeclampsia, and fetal growth restriction. Women at high risk for those outcomes should be identified in early pregnancy.

Key words: aspirin, fetal growth restriction, meta-analysis, meta-regression, preeclampsia, pregnancy, systematic review

PREVENZIONE?

CONCLUSIONI

- Le gravidanze ottenute con ovodonazione presentano un aumentato rischio di complicanze ostetriche e perinatali, in particolare disordini ipertensivi della gravidanza e preeclampsia
- La ragione è presumibilmente da ascrivere ad una serie di meccanismi di alterata tolleranza immunologica nei confronti dell'ospite, della madre contro il feto
- Prima di intraprendere queste procedure è ragionevole esporre alla futura gestante questi rischi
- Per queste caratteristiche la gravidanza ottenuta con ovodonazione deve essere seguita da personale adeguatamente formato nella prevenzione delle complicanze e nel monitoraggio di gravidanze ad alto rischio
- Devono essere messe in atto tutte le strategie di monitoraggio atte ad identificare precocemente le complicanze
- Il ruolo preventivo di basse dosi di aspirina nella prevenzione della preeclampsia in assenza di altri fattori di rischio deve essere attentamente valutato e richiede ulteriori studi clinici.

….GRAZIE PER L'ATTENZIONE.